Recurrent cerebrovascular ischaemic events in patients with interatrial septal abnormalities: a follow-up study

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Abstract The aim of this study was to evaluate the risk of recurrent ischaemic cerebrovascular events (stroke or transient ischaemic attack (TIA)) in patients with patent foramen ovale (PFO) or atrial septal aneurysm (ASA) treated with different therapeutic regimens. We enrolled 86 patients aged 18–60 years with an unexplained ischaemic stroke or TIA referred to our inpatient department in the period May 1994–December 1999. Follow-up lasted until April 2003. Patients were excluded if the stroke or TIA was related to large-artery atherosclerosis, small artery occlusion, major cardiac sources of embolism or other uncommon causes. During a follow-up (mean±SD) of 64.1±28.8 months (range 8.1–105.6) a recurrent ischaemic cerebrovascular event occurred in 11/86 patients (12.8%) (5 TIA and 6 strokes). Eight events (4 TIA, 4 strokes) occurred in the 59 patients with PFO alone, three (1 TIA, 2 strokes) in the 21 with PFO plus ASA and none in the 6 patients with ASA alone. In the overall population the cumulative risk of recurrent stroke/TIA was 1.2% at 2 years, 5.5% at 4 years, 7.6% at 6 years and 23.6% at 8 years, and was similar in patients with PFO alone *vs*. patients with PFO plus ASA (9.0% *vs*. 6.1% at 6 years, 26.0% *vs*. 23.1% at 8 years; $p>0.05$). Nine cerebral ischaemic events (4 TIA, 5 strokes) occurred in the 48 patients treated with antiplatelet drugs (7 in patients with PFO, 2 in patients with PFO plus ASA), and two (1 TIA, 1 stroke) in the 17 patients treated with oral anticoagulants (1 with PFO, 1 with PFO plus ASA). No events occurred in patients submitted to transcatheteral closure.

Key words Stroke • Patent foramen ovale • Prevention

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Introduction

In the last decade the role of patent foramen ovale (PFO) and atrial septal aneurysm (ASA) in the aetiopathogenesis of ischaemic stroke has been largely investigated [1]. Several studies have estimated the recurrence risk of stroke or transient ischaemic attack (TIA) in patients with PFO. Comess et al. found a high rate of recurrent ischaemic cerebrovascular events (ICVE) in patients with ASA or interatrial shunt [2]. A recurrence rate of 3.4% per year was reported by Mas and Zuber [3], similar to the 3.8% per year of the casistic from Bogousslavsky et al. [4]. A recent large prospective study has reported that the frequency of recurrent stroke is low in patients with isolated PFO treated with aspirin [5]. Moreover, the coexistence of ASA identified a subgroup in which preventive strategies other than antiplatelet drugs such as oral anticoagulants, surgical or transcatheteral closure of PFO have to be considered [5]. However there are no clear-cut data on what solution is better in the management of patients with PFO plus ASA [6–9]. In the present work we have estimated the risk of recurrent ICVE (stroke or TIA) in patients with PFO or ASA treated with different therapies.

Patients and methods

Case study

We enrolled 86 patients aged 18–60 years with unexplained ischaemic stroke (defined as a neurologic deficit that lasted more than 24 h) or TIA with the presence of PFO or ASA. These patients were referred to our inpatient department (First Division of Neurology, San Giovanni Battista Hospital, Turin, Italy) in the period May 1994–December 1999. Follow-up lasted until 30 April 2003.

Data collection

Stroke risk factors, previous vascular history, clinical and instrumental findings, and stroke severity [10] were systematically recorded. Cranial CT scan was performed at admission. If negative, a second CT scan was performed 48 h after onset. Brain MRI was performed in 50% of the cases, in patients with TIA and if the second cranial CT scan failed in revealing an ischaemic lesion related to the clinical picture.

All patients underwent a standardised diagnostic workup to highlight definite causes of stroke. Diagnostic protocol consisted of routine blood examinations, complete coagulation screening (including tests for protein S, protein C and antithrombin III deficiency and antiphospholipid antibodies), 12-lead electrocardiogram, transthoracic and transoesophageal echocardiogram. Also, an extracranial duplex ultrasonography (100%), a conventional (20%) or a MR angiography (40%) were performed within one month of the onset. Additional investigations, namely to detect asymptomatic deep vein thrombosis, were left to the discretion of the physicians as failure to document venous thrombi does not exclude paradoxical embolism in PFO patients [11]. Patient were excluded if the diagnostic workup revealed the following causes of stroke defined according to TOAST criteria [12]: (1) large-artery atherosclerosis (defined as >50% stenosis or occlusion of the corresponding vessel); (2) small artery occlusion stroke (defined as a small deep infarct less than 15 mm in diameter in a patient with hypertension or diabetes); (3) major cardiac sources of embolism, such as atrial fibrillation, recent (within four months before the stroke) myocardial infarction, dilated cardiomyopathy, mitral stenosis, mitral or aortic vegetations or prosthesis, left atrial or left ventricular thrombus or tumour, spontaneous echo contrast in the left atrium, akinetic left ventricular segment and complex atheroma of the aortic arch; (4) other definite causes of stroke, such as nonatherosclerotic arteriopathies (e.g., dissection), coagulopathies (e.g., the antiphospholipid–antibody syndrome) or systemic disorders(e.g., migrainous infarction). Clinical and imaging data were reviewed by two neurologists unaware of the echocardiographic findings.

Echocardiography

All patients underwent transthoracic and transoesophageal echocardiography, performed by experienced cardiologists according to the protocol reported in our previous study [13]. Examinations were recorded on videotape and reviewed by two independent examiners unaware of the patients' clinical data and outcome.

According to our previous work [13] and to other Authors [15–17], the entity of the right-left shunt was defined "small" if less than 20 microbubbles appeared in the left atrium upon release of a Valsalva manoeuvre and "large" if at least 20 microbubbles appeared after Valsalva or if a right to left shunt was evident at rest. An ASA was diagnosed when the atrial septum extended at least for 11 mm either into the left or the right atrium or both.

Treatment and follow-up

Each physician autonomously decided which therapy (antiplatelet drugs or anticoagulant) to employ. In general, according to current recommendations [14], patients with small or isolated PFO were preferentially treated with antiplatelet drugs while patients with large PFO or PFO associated with ASA were preferentially treated with oral anticoagulants. Transcatheteral closure of the anomaly was considered in the presence of: (a) recurrent events during drug treatment; (b) multiple non-lacunar ischaemic areas on neuroimaging; (c) right-left shunts classified as "large entity shunt" or associated with ASA. Patients were annually evaluated by an expert neurologist (70% of the cases) or, if not possible, by phone interview (30% of the cases). The following endpoints were systematically recorded: recurrent stroke or TIA, peripheral embolism, myocardial infarction and death.

Antiplatelet drugs were started during the acute phase whereas anticoagulants were initiated (mean±SD) 21±10.7 days after the first event with no significant differences among the three groups.

Statistical analysis

Chi-square test, Fisher's exact test, *t*-test for unpaired data and variance analysis were employed where appropriate. Kaplan-Meier survival curves were applied to assess the risk of recurrent stroke/TIA according to different subgroups. Differences among groups were explored by the logrank test. The predictive value of each atrial septal defect (PFO alone, ASA alone, PFO plus ASA) and of the shunt entity with respect to recurrent stroke/TIA was assessed using the Cox proportional-hazard model. All tests were two-tailed and the significance level was defined as $p<0.05$.

Results

Study population

The 86 patients [age (mean±SD): 45±13.5 years; 43 males, 43 females) were divided into three groups according to the atrial septal abnormality: 59 patients had PFO alone, 6 had ASA alone, and 21 had PFO and ASA. Baseline features and vascular risk factors of the patients are detailed in Table 1. There were no significant differ-

Table 1 Baseline characteristics, and vascular risk factors and treatment in patients with atrial septal abnormalities

	PFO n (%)	PFO+ASA n (%)	ASA n (%)	Total (%) n (%)	*p* value
	59 (68.6)	21 (24.4)	6 (7)	86 (100)	
Males	30 (51)	9 (43)	4 (66.6)	43 (50)	NS
Age ≤55 years	48 (81.4)	14 (66.7)	3 (50)	65 (75.6)	NS
Age >55 years	11 (18.6)	7 (33.3)	3 (50)	21 (24.4)	NS
Age mean (years)	42.7±12.5	49.1±15.4	52.8±9.8	45.0±13.5	
Hypertension	13 (24.5)	3 (14.3)	2 (3.3)	18 (22.5)	NS
Diabetes	2 (4)	2 (9.5)	1 (16.6)	5 (6.25)	NS
Dyslipidaemia	11 (21)	1 (5)	1 (16.6)	13 (16.25)	NS
Smoke	19 (36)	8 (38)	1 (16.6)	28 (35)	NS
Stroke	41 (69.5)	14 (66.7)	5 (83.4)	60 (69.8)	NS
TIA	14 (23.8)	7 (33.3)	1 (16.6)	22 (25.6)	NS
Shunt <20 bubbles	32 (54.2)	10 (47.6)	–	42 (52.5)	NS
Shunt >20 bubbles or at rest	27 (45.8)	11 (52.4)	–	38 (40)	NS
Antiplatelets	38 (64.5)	6 (28.7)	4 (66,7)	48 (55.8)	
Oral anticoagulants	7 (11.8)	8 (38.0)	2 (33.3)	17 (19.8)	
TCC	14 (23.7)	7 (33.3)	0	21 (24.4)	
Mean follow-up (months±SD)	62.7±29.9	63.5±28.0	79.6±15.5	64.1±28.8	

TCC, transcatheteral closure

ences among the three groups. About 24% of the PFO patients also had an ASA whereas most of the ASA patients (77.7%) also had a shunt. About three-quarters of the patients were aged less than 55 years. A large shunt was evidenced in 52.4% of patients with PFO plus ASA *vs*. 45.8% of patients with PFO alone ($p>0.05$). Starting from the employed treatment, the study population was divided into three groups. Group A included patients treated with antiplatelet drugs (48 cases: 38 with PFO alone, 6 with PFO plus ASA, 4 with ASA alone). Group B included patients treated with oral anticoagulants (warfarin with target INR of 2–3) (17 cases: 7 with PFO alone, 8 with PFO plus ASA, 2 with ASA alone). Group C included patients who underwent transcatheteral closure (21 cases: 14 with PFO alone, 7 with PFO plus ASA).

Recurrent events

The Kaplan-Meier estimation of the risk of a second cerebral ischaemic event (stroke/TIA) according to atrial septal defects is shown in Table 2 and Fig. 1. During a follow-up (mean±SD) of 64.1±28.8 months (range 8.1–115.6), a second event occurred in 11/86 patients (12.8%) (5 TIA and 6 strokes).

Eight events (4 TIA, 4 strokes) recurred in the 59 patients with PFO alone, three (1 TIA, 2 strokes) in the 21 with PFO plus ASA and none in the 6 patients with ASA alone.

In the overall population the cumulative risk of recurrent stroke/TIA was 1.2% at 2 years, 5.5% at 4 years, 7.6% at 6 years and 23.6% at 8 years, and was similar in

Table 2 Kaplan-Meier estimation of the risk of a second ICVE, according to atrial septal abnormalities

	N	ICVE	Mean follow-up (years)	Cumulative risk (%)			
				At 2 years	At 4 years	At 6 years	At 8 years
PFO	59	8 (13.5%)	4.7	1.8 (0–4.1)	6.0 (2.6–9.4)	9.0 (4.6–13.4)	26.0 (16.4–35.6)
PFO+ASA	21	3 (14.2%)	4.3	0	6.1 (0.2–12)	6.1 (0.2–12)	23.1 (6.9–39.3)
ASA	6	0	5.2	0	0	0	0
TOTAL	86	11 (12.7%)	4.7	1.2 (0–2.8)	5.5 (2.8–8.2)	7.6 (4.3–10.9)	23.6 (15.8–31.4)

ICVE, ischaemic cerebrovascular events (stroke or TIA)

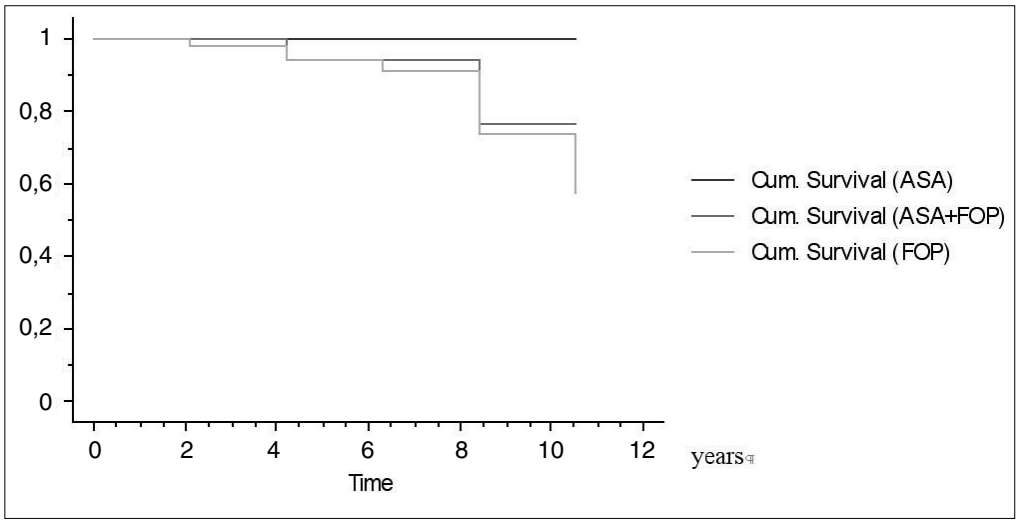


Fig. 1 Kaplan-Meier curve (probability to remain free from a second ICVE) according to atrial septal abnormalities

patients with PFO alone versus patients with PFO plus ASA (9.0% *vs*. 6.1% at 6 years, 26.0% *vs*. 23.1% at 8 years; $p>0.05$). As no stroke/TIA event occurred in patients with isolated ASA, the cumulative risk of recurrence was zero (no event occurred in this group).

Cox analysis (Table 3) revealed that the presence of ASA or PFO – both isolated and associated – was not associated with an increased risk of recurrent stroke/TIA. Nevertheless, there was a clear trend for large shunts (as defined in the Methods section) to predict an increased risk of recurrent stroke/TIA (hazard ratio: 1.87; $p=0.05$). Neither gender nor age were predictors of recurrent cerebral ischaemic events.

Effect of treatment

Kaplan-Meier estimation of the risk of a second stroke/TIA according to the different treatments is detailed in Table 4 and Fig. 2. Nine cerebral ischaemic events (4 TIA, 5 strokes) occurred in the 48 patients treated with antiplatelet drugs (7 in patients with PFO, 2 in patients with PFO plus ASA), and two (1 TIA, 1 stroke) in the 17 patients treated with oral anticoagulants (1 with PFO, 1 with PFO plus ASA). No events occurred in patients submitted to transcatheteral closure. With respect to the whole population, 18.7% of the antiaggregant-treated patients and 11.7% of the anticoagulant-treated reported a recurrent stroke/TIA.

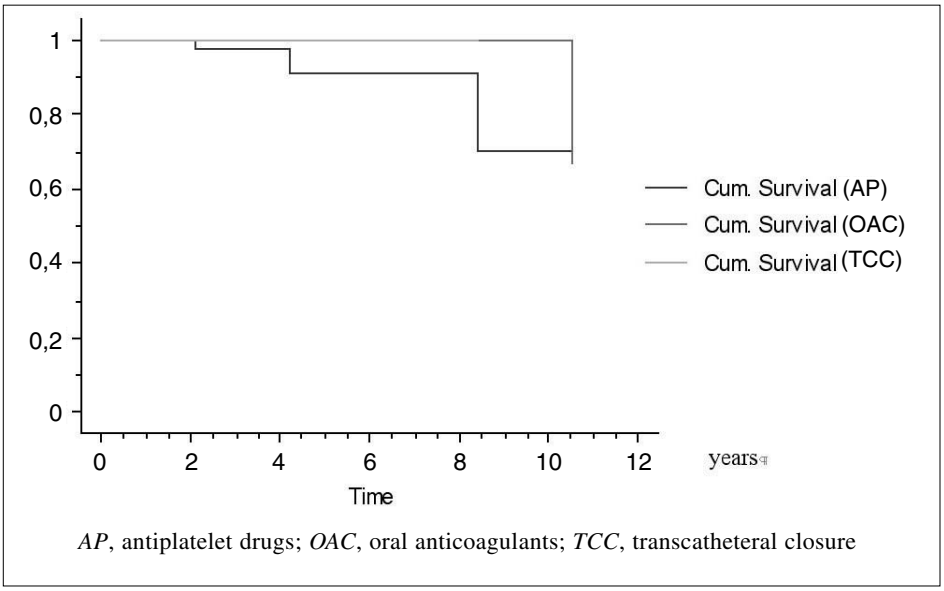
Table 3 Cox proportional-Hazard models of the predictors of a second ICVE in patients with atrial septal abnormalities

	Hazard ratio	(95% CI)	*p* value
Age	1.07	0.97–1.06	NS
Male sex	1.67	0.40–6.82	NS
PFO alone	1.33	0.15–11.5	NS
ASA alone	1.19	0.16–8.7	NS
PFO and ASA	1.39	0.15–12.8	NS
Shunt >20 bubbles or at rest	1.87	0.96–3.66	0.05

Table 4 Kaplan-Meier estimation of the risk of a second ICVE, according to different therapies

	n	ICVE	Mean follow-up (years)	Cumulative risk (%)			
				At 2 years	At 4 years	At 6 years	At 8 years
Group A: AP	48	9 (18.7%)	4.8	2.1 (0–4.6)	8.7 (4.5–13.2)	8.7 (4.5–13.2)	29.6 (19.9–49.5)
Group B: OAC	17	2 (11.7%)	4.6	0	0	0	23.2 (5.9–40.5)
Group C: TCC	21	0	2.6	0	0	0	–

AP, antiplatelet drugs; *OAC*, oral anticoagulants; *TCC*, transcatheteral closure



AP, antiplatelet drugs; *OAC*, oral anticoagulants; *TCC*, transcatheteral closure

Fig. 2 Kaplan-Meier curve (probability to remain free from a second ICVE) according to the different therapies

The cumulative risk of recurrence was not significantly different in group A versus group B (29.6% and 23.2 % respectively). Kaplan-Meier estimation of the risk of a second stroke/TIA with respect to the type of atrial anomaly and the treatment is detailed in Table 5. The highest likelihood of recurrence was found in patients with PFO plus ASA treated with antiplatelet drugs (cumulative risk of 20% at 4 years, 73% at 8 years). In anticoagulant-treated patients with PFO plus ASA, antiaggregant-treated patients with PFO alone and anticoagulant-treated patients with PFO alone the cumulative risk of recurrence was similar (21.6%, 27.1% and 24.8% at 8 years, respectively; $p>0.05$). No event was reported in patients submitted to transcatheteral closure [follow-up (mean±SD) 33.2.±17.3 months].

Table 5 Kaplan-Meier estimation of the risk of a second ICVE, according to atrial septal abnormalities and the different therapies

	N	ICVE	Mean follow-up (years)	Cumulative risk (%)			
				At 2 years	At 4 years	At 6 years	At 8 years
PFO (AP)	38	7	4.8	2.6 (0-5.7)	8.1 (3.6-12.6)	8.1 (3.6-12.6)	27.1 (16.7-37.5)
PFO (OAC)	7	1	4.6	0	0	0	24.8 (6.1-43.5)
PFO (TCC)	14	0	2.5	0	0	0	-
PFO total	59	8	4.7	1.8 (0-4.1)	6.0 (2.6-9.4)	9.0 (4.6-13.4)	26.0 (16.4-35.6)
PFO+ASA (AP)	6	2	4.8	0	20.0 (2.1-37.9)	20.0 (2.1-37.9)	73.3 (48.7-97.9)
PFO+ASA (OAC)	8	1	4.6	0	0	0	21.6 (12.5-30.7)
PFO+ASA (TCC)	7	0	2.6	0	0	0	-
PFO + ASA total	21	3	4.3	0	6.1 (0.2-12)	6.1 (0.2-12)	23.1 (6.9-39.3)
ASA (AP)	4	0	5.3	0	0	0	0
ASA (OAC)	2	0	5.0	0	0	0	-
ASA (TCC)	0	0	0	-	-	-	-
ASA total	6	0	5.2	0	0	0	-
TOTAL	86	11	4.7	1.2 (0-2.8)	5.5 (2.8-8.2)	7.6 (4.3-10.9)	23.6 (15.8-31.4)

ICVE, ischaemic cerebrovascular events (stroke or TIA); *PFO*, patent foramen ovale; *ASA*, atrial septal aneurysm

Discussion

In our study the cumulative risk of stroke/TIA was 1.2% at 2 years, 5.5% at 4 years, 7.6% at 6 years and 23.6% at 8 years with a mean annual rate of 2.9%, with no significant differences between patients with PFO alone and those with PFO plus ASA. However, the presence of a large shunt may represent a predictor of increased risk of recurrent stroke/TIA. The significance of the high risk of recurrence at 8 years (23.6%) is limited by the small number of patients.

In patients with stroke or TIA without arterial and major cardiac sources of embolism in a previous work we found a frequency of PFO of 31.4% that rose to 40.6% in patients with non-lacunar (presumably embolic) stroke/TIA [13]. Reported rates of PFO occurrence in patients with cryptogenic stroke range from 31 to 77% [1].

In this study, we selected patients aged less than 60 years because the higher prevalence of large-vessel atherosclerosis or small-artery disease in the elderly population makes the diagnosis of cryptogenic stroke less probable. Notably, most of our patients were aged less than 55 years and the association of PFO with cryptogenic stroke has been consistently reported in this age group [1]. Little data are available on the recurrence of cerebral ischaemic events (stroke/TIA) in patients with PFO and ASA.

Comess et al. observed a high rate of recurrent ICVE in patients with either ASA (16.9/100 person-years) or right-left atrial shunt (14.4/100 person-years) [2]. No difference in frequency of patients taking aspirin or warfarin was reported but the actual therapy was not reported in detail.

In the Lausanne study, during a mean follow-up of 3 years, the rate of recurrent events was 3.8% per year in 135 patients with PFO and/or ASA independent from the employed strategies (antiplatelet drugs, anticoagulants or surgical closure) [4]. A French study prospectively evaluated 132 patients with PFO, ASA or both (126 of whom received antiplatelet drugs or anticoagulants) for 22.6 months [3]. Their average annual rate of stroke/TIA was 3.4% and the association of PFO plus ASA was particularly ominous.

A number of reports have recently emphasised the size of the right to left shunt as the crucial factor for paradoxical embolism in stroke patients [15–18].

More recently, De Castro et al. reported a higher recurrence risk (12.5%) at 3 years in the subgroup of patients with right-left shunt at rest or with "high interatrial membrane motility" [19].

Despite these results, the better preventive strategy for stroke patients with PFO or ASA is yet to be established [20]. The absolute risk of recurrent stroke/TIA in patients with PFO is low according to different retrospective studies [20]. Usually, these patients are empirically treated with antiplatelet drugs, anticoagulants, transcatheteral or surgical closure of the septal defect. Current available guidelines suggest anticoagulants or transcatheteral closure in patients at higher risk (PFO plus ASA, large PFO, multiple infarction) [14]. In the present study patients with PFO alone were at low risk of recurrent stroke/TIA independently from the employed therapy (antiplatelet drugs or anticoagulants). Anyway, the value was not negligible because about 3% of patients experienced a new cerebrovascular event. No event recurred in patients with ASA alone. There was no difference in the risk of recurrence between patients treated with antiplatelet drugs *vs*. oral anticoagulant but patients with PFO plus ASA treated with antiplatelet drugs showed a high likelihood of recurrence with a cumulative risk of 20% at 4 years and of 73% at 8 years.

In the prospective study by Mas et al. [5] secondary prevention with aspirin was found to be insufficient in young patients with isolated PFO and a single unexplained stroke. They also reported that patients with PFO plus ASA represented a subgroup with a higher risk of recurrent stroke that could benefit from more aggressive therapeutic strategies (long-term anticoagulation, surgical or transcatheteral closure of the PFO).

In the recent PICCS study the high prevalence of PFO with cryptogenic stroke was confirmed: neither the PFO size nor the association with ASA conferred an additional risk of recurrent events and the recurrence rate was similar in patients randomised to anticoagulant and to antiaggregant therapy [21].

In our study no recurrent stroke/TIA occurred in the 14 patients submitted to transcatheter closure during a mean follow-up period of 33 months. It is noteworthy that these patients were considered at high risk because of a "large" shunt or multiple ischaemic lesions. In the initial experience with surgical closure, Devuyst et al. reported no recurrent event in 32 patients [22], but papers by Homma et al. (19.5% recurrence rate at 13 months) and the Mayo Clinic (7.5% at 1 year and 16.6% at 4 years) were disappointing [23, 24].

Surgery has been superseded by the percutaneous transcatheteral approach due to the absence of open-heart surgery [25]. After early experiences in which the success in the reduction of ischaemic events was balanced by a high rate of periprocedural complications, subsequent studies using multiple device systems have demonstrated similar rates of recurrent thromboembolic events [26–33].

The rate of recurrent cerebral ischaemic events was 3.2% per year in the 63 patients treated by Hung et al. [32]. In the case report of Meier et al. [33], the actuarial freedom from recurrent embolic events was 95.1% at 1 year, decreased to 90.6% at 2 years and remained stable thereafter (90.6% at 6 years). The present study has some limitations. Although its follow-up period was longer with respect to most literature reports, it was not a randomised study. Besides, the follow-up was shorter for patients sub-

mitted to transcatheteral closure and the number of cases in each treatment group was low to gain definite indications on the best treatment to reduce recurrent stroke/TIA. Anyway, our results seem to confirm the high risk of recurrence in patients with PFO plus ASA if treated with antiaggregants and the importance of an accurate diagnostic work-up to exclude any determined cause of ischaemic stroke. Moreover our data confirm the safety of transcatheteral closure, which is a reasonable alternative therapy in the prevention of presumed paradoxical embolism in the presence of an atrial septal abnormalities [34, 35].

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